dialogue on HPV-DNA testing as a screening method for cervical cancer and giving me this opportunity to comment. Dr. Lorincz has already summarized the data from our South African study as well as that from a number of other large studies. These studies have clearly shown that HPV-DNA testing is more sensitive than is a conventional Pap smear for detecting high-grade cervical disease.

What I would like to do is just make a couple of brief comments about the applicability of our South African data to studies in the United States and also about HPV-DNA testing in general.

[Slide.]

We selected Cape Town for our study because it was a large unscreened population. As a result, there was a very high prevalence of cervical disease there. 3 percent of all of the women screened had high-grade cervical disease, either high-grade CIN or cancer. This means that we could evaluate the feasibility of using HPV-DNA testing in a relatively small population of women, much smaller than would be required in the United States.

However, in my opinion, the results of the Capetown study are applicable to other high-risk populations in the United States. The University of Capetown cytology laboratory is staffed by excellent cytologists. They are equivalent to those seen in a service laboratory in the

United States.

My collaborators in South African was a GYN oncologist who was an expert colposcopist, again as good as you would find in the United States. All histology was read by GYN pathologists in the United States and the HPV-DNA testing that was done in this laboratory in South Africa was done by technicians trained at Digene and, again, was QCd by technicians in the United States.

[Slide.]

In Capetown, we observed a lower specificity of HPV-DNA testing for high-risk types of HPV than was observed in most of the other studies reported today. This specificity of HPV-DNA testing was 82 percent even though the women enrolled were over the age of 35.

It needs to be pointed out, however, that this was a particularly high-risk population of women and the specificity of cytology was also low. It was 88 percent. It was high risk because 2.4 percent of the women had biopsy-confirmed high-grade CIN. 7.4 percent of these women were HIV seropositive. 5.6 percent were infected with either Chlamydia or gonorrhea and 19 percent of the women had culture-proven Trichomonas.

So this was a very high-risk population which explains why we think there was a high prevalence of HPV-DNA positivity in it.

[Slide.]

HPV-DNA testing has a number of advantages compared to cytology. The first is that HPV testing is more sensitive than conventional cytology. Increased sensitivity is important for screening high-risk populations in the United States who may participate only sporadically in screening programs.

A second advantage is that HPV-DNA testing can be performed on patient-collected samples. Most women who develop cervical cancer, as Dr. Kinney has already shown you, in the United States, have not had a Pap smear within the last three to five years, but many of these women have had access to primary healthcare facilities.

If HPV-DNA testing of patient-collected samples could be included in the regular periodic health exams of older women, we would be able to increase screening coverage of these women in the United States.

The third advantage is that not only does HPV-DNA testing tell us who has disease today but it predicts who will develop disease in the future, which is very important for designing screening strategies. It is also important because it allows women to know what their risk is of developing cervical disease in the near future.

[Slide.]

When we talk about cytology screening programs in

the United States, we often forget that there are some segments of our population who do not receive regular cytology screening and, as a result, are at risk for developing cervical cancer.

This data from the CDC on Pap-smear screening demonstrates much lower screening rates in poor and older women. For example, almost 14 percent of the women in the CDC study between the ages of 50 and 59 had a last Pap smear more than five years before.

[Slide.]

This results in high rates of cervical cancer among certain segments of the population. For example, blacks and Hispanics living in New York City have an almost 70 percent greater risk of developing cervical cancer than does the average women living in New York State because they do not have access to screening.

Because of its ability to increase the detection of high-grade lesions in women being only sporadically screened has potential to extend screening coverage for women not having speculum exams. I strongly support the use of HPV-DNA testing as a method for primary screening in women over the age of 30 in the United States.

Thank you very much for this opportunity.

DR. WILSON: Thank you, Dr. Wright.

Our final presentation will be by Ms. Poole who

will read portions of a letter from Dr. James Linder who is Professor of Pathology and Microbiology at the University of Nebraska Medical Center.

MS. POOLE: Thank you, Dr. Wilson. We received a letter from Dr. James Linder who is a Professor at the University of Nebraska Medical Center. He states that he also serves as a consultant to Cytyk Corporation who is the manufacturer of the ThinPrep Pap test. However, these statements and comments are his own and not those of Cytyk Corporation.

In the interest of time, I will just read a few of the salient points that he made, but the entire letter is included in the handouts that you have.

Dr. Linder states that he supports HPV testing as an adjunct to morphologic cytology and believes the role for HPV assays or assessments of other molecular markers will grow. He states that using the Pap smear as a measure of HPV test sensitivity may not be appropriate considering the lower sensitivity of the smear method as compared to the ThinPrep method.

He further states that if HPV testing is used as a screening agent, as opposed to reflex testing of ASCUS paps, the HPV testing platform would have high specificity for the recognized high-risk types of human papilloma virus.

He encourages the Food and Drug Administration to

at

obtain comments from other public and medical community and other professional organizations before we develop guidance for these types of devices

Thank you.

DR. WILSON: Thank you, Ms. Poole.

Would any other members of the public like to comment at this time? In the interest of time, then, I think we would like to hold any questions at this point. We would like to members of the public who have commented to return for the sessions later this afternoon. We might be able to ask questions of them then.

We are running a bit behind schedule so we would like to break for lunch now. We would like to reconvene at ten minutes after the hour. Thank you.

[Whereupon, at 12:25 p.m., the hearing recessed, to reconvene at 1:10 p.m., this same day.]

A F T E R N O O N P R O C E E D I N G S

[1:20 p.m.]

DR. WILSON: I would like to reconvene the meeting at this time. I would like everyone to be aware that we have to vacate this room at 4:30 today because there is another function in here immediately thereafter. So we are going to ask all the speakers to be as much on time as possible and we will probably not take a break in the interest of time.

Our next speaker is Dr. Penny Hitchcock who is the Chief of the Sexually Transmitted Diseases Branch of the National Institute of Allergy and Infectious Diseases.

Dr. Hitchcock.

NIH Presentation

DR. HITCHCOCK: Thank you very much. I appreciate the opportunity to comment. First, I am going to tell you that, having prepared my talk in isolation of the other excellent talks that were given today, I am going to skip over some of the things--the points have already been made--and get to what I think are some very difficult issues that, for the most part, have not been articulated.

[Slide.]

I want to unequivocally state my position here with respect to sexually transmitted diseases, HPV infection and cervical cancer. I think this is an enormously

important healthcare problem. I think there is absolutely no double that HPV causes cervical cancer.

That said in a country where we have the highest rates of STDs of any developed country in the world, yet we do the best job, really, of any country with this particular sexually transmitted disease and its manifestation.

I think we have to ask ourselves why do we spend upwards to $6 billion a year to save the lives of the 14,000 women who will be diagnosed this year with cervical cancer. We do save the lives of most of those women. Only 4,000 to 5,000 a year die. I don't want to break that. I don't want to do anything to diminish the track record that we currently have, and my personal objective in this is to stand up here soon and be able to tell you that no women die of cervical cancer in this country.

So we have an unusual situation where the United States is actually at a great record for this particular sexually transmitted disease. In the developing world, as you have heard, this is not the case. A quarter of a million women a year die of cervical cancer and, since the start of the AIDS epidemic, which people incorrectly say the first fatal STD, we have seen 20 million women die.

So what can we do in the developing world to bring those numbers down to the point where they look like our numbers, where we know we are not going to be able to spend

that sort of money to achieve the same track record.

So my talk is really to look at some of the issues that are in front of us now that we are, a, absolutely certain of the role of HPV in cervical cancer and, b, have an excellent test to tell us about the HPV status of women.

So let me move ahead.

[Slide.]

Papanicolaou, when he developed the Pap smear, I can assure you, had absolutely no idea he was looking for the manifestation of a sexually transmitted virus. The test was developed in 1948 and we had astronomical deaths in this country due to cervical cancer. It was the most common cancer killer of women.

From '55 to '92, we experienced a 74 percent decrease in mortality related to this disease. It is true, everything you have heard about the Pap smear test not being as sensitive as it needs to be. The question is, why does it work so well?

It works well because women are committed to getting an annual Pap smear. When you habitually use a relatively insensitive test, what you do is you increase the positive predictive value of that test so that, indeed, the Pap smear has led us to a change in survival rates.

If the disease is caught early, we have a 91 percent survival, overall a 70 percent survival and, if

we get it in the preinvasive stages, 100 percent survival. So, from '73 to '95, and that lag between '55 when it was implemented, represents how long it has taken to get good coverage and good use of this.

We have seen a 43-fold decrease in the incidence of cervical cancer due to this test.

[Slide.]

The link to HPV infection is stronger than lung cancer to cigarettes. However, as people have said again and again, it requires persistent infection. The number of sex factors and, importantly, the failure to Pap-smear screen regularly are the things that will count heavily against a women's chances of escaping consequences.

[Slide.]

Let's, for a second, talk about HPV infection in men because, clearly, that is where women get the infection. We have one study to suggest that lesbian women do have HPV infection. However, most of those women are in partnerships where at least one of the partners is bisexual and it isn't clear whether or not two women who have always been involved in women who have sex with women can, in fact, get HPV infection.

So the infection comes from men. It is almost always silent. We can find HPV-DNA in ejaculate. We can occasionally find white lesions. We can occasionally find

things that really look like warts but it is really only in the immune-compromised host, and this means mostly the HIV-positive men, where we see anal cancer and penile cancer.

Again, the breakthrough with Joel Puleski's work showing that a Pap smear of the anus can really make an important contribution to prevent disease and death due to anal cancer in those men.

So I think it is important to realize that we can't find the infection in men. So when we talk about the consequences of detecting HPV infection, we are really talking about consequences that women are going to bear. There are good consequences and there are some negative consequences.

[Slide.]

To control cervical cancer right now in this country, it is within our grasp. Of the 12,800 cervical cancer diagnoses in 2000, 4,600 women will die. In fact, the biggest risk factor for those women is that they haven't had a Pap in three years.

[Slide.]

This is a health disparity issue. Although the prevalence of human papilloma virus is high among all women who live in this country, the cancer rates are not. That has to do with who is Papped and, importantly, who has access to follow-up care if they have a diagnosis that

requires follow up.

Overall, the incidence of cervical cancer is 8 per 100,000, age-adjusted. In Native Americans, Koreans and Hispanics, it is 15. In Japanese Americans, it is 5.8. In Vietnamese, it is 43.

[Slide.]

In terms of death rates here, again, we are talking about a health disparity that means not only are women not getting Papped but, importantly, if they are, they are not getting follow up. So we see a death rate of 2.5 per 100,000 in U.S. women and 6.7 per 100,000 in African-American women.

[Slide.]

The current recommendations are that a women be Papped at 18. That I think we need to look at because we know that young people are becoming sexually active at 11, 12, 13. In fact, in a recent study, girls 11 to 13 who become sexually active are most likely, a third of them, to have sex with a man who is five years older than they are which may explain the high attack rate in young girls.

If you have three consecutive normal findings, then your physician decides, based on other issues, what your frequency of Pap-smear screening should be. There is no upper age limit in this country. Medicare benefits cover Pap every three years. Importantly, in most countries in

Europe, the first Pap is recommended at 30 years of age which brings us close to the question that we are asking today, and that is is there a role for HPV testing in women at 30.

[Slide.]

There is research, obviously, on new diagnostic tests and we are soon going to hear about ALTS study which I think is a key piece of information for us to truly consider the question in front of us.

The Digene test, as you know, is approved for ASCUS only and, again, I want to make it clear that I am totally supportive of the use of that test to differentiate between an atypical cell, atypical Pap, with undetermined significance.

We, in fact, have worked with Digene and other companies to develop approaches to self-administered vaginal swabs which would be used for Paps as well as HPV detection. In fact, in resource-limited settings, I think there is a clear need for some triage of involving HPV testing, a rapid, simple, easy-to-use test and follow up with Paps if there is persistent infection.

So I think there are, certainly, research issues here that are moving forward.

[Slide.]

If we could ordain that only women 30 and older

would be Pap-smear screened and/or HPV tested, much of the arguments I am going to lay in front of you would be moot. But the truth is is that I think I we have, for the most part, an uneducated physician community and a very poorly educated consumer community who is--right now, young women in particular, they are terrorized at the idea that they have a sexually transmitted infection.

They don't know what it means. They are very angry that their doctors haven't told them they have that infection, even though many of their doctors didn't know it until very recently, and they want to know who gave it to them.

At this time, this infection, and you saw the pyramid earlier that appears in the text book on STDs--at this time the infection is so prevalent that you would almost test off a list. We could put everybody on a list who is of reproductive age and if you thought you were uninfected, would could give you a test and then the burden of proof would be on you to show us that you weren't infected.

If you have had sex with more than one partner in your lifetime or your partner has had sex with more than one partner, the chances that you have been infected once in your life are outstanding.

In terms of public health, there is virtually

little to be learned if we should screen and test and you have to understand that there are people in our Congress that moved forward this year with legislation to make HPV a reportable infection. What would that mean? It would mean that women who were HPV-positive--and it would only mean women who were HPV-positive--would end up on that list by having abnormal Pap.

What a way to discourage women from being Papped. I will tell you one thing. The first time a disease intervention specialist came to my door and wanted to know who my sexual partners were based on my positive Pap smear, I would think twice about going to be papped again because most women get Papped annually and it is only occasionally that you have an abnormal Pap.

The point I am trying to make here is that this is extremely useful information as soon as we figure out what to tell women about it and what we are going to do about it.

I skipped over the condom slide. Having been involved in a recent workshop, I can tell you there are a lot of studies that have attempted to look at the role of condoms to prevent HPV transmission. There are not enough good studies and not enough evidence to answer that question. That means you can neither tell women the condom won't work or tell them to use the condom to prevent it because we don't know the answer.

I am also afraid, frankly, that as younger people, under 30, ask for and are given this test, that physicians are going to be put in the position of intervening. It is already happening. Ablative steps are being done for women with early lesions instead of waiting to see what happens because we don't have an educated provider population here.

I am worried that we will compromise these women, their fertility, when they have a positive Pap at 17, 18 years of age where most of these women, if we waited, the body's normal immune response to this infection would cause that lesion to regress.

[Slide.]

Again, this is headed towards being a reportable disease depending upon the lay of the land with respect to our next administration. Infection, per se, does not correlate with disease. It is usually self-limiting. We can't prevent transmission except abstinence which, for our species, is not a lifelong tenable way to prevent sexually transmitted diseases.

Condoms. Big question mark. A great study that just came out in the journal STD last month suggests that we may actually see some protection against cervical infection with use of condoms but we don't know that. No men will be on this list of reportable diseases except for gay men who are already being persecuted because of their HIV status.

It will be women with positive Paps.

[Slide.]

So, finally, cervical cancer is a preventable disease and I think our highest priority in this country is to eliminate it as a cause of cancer deaths for women, to do some research to understand how to position it in this country, and to do a lot of research to use it as a tool in conjunction with HPV screening for the developing world.

We, I think, are going to see breakthroughs in terms of prevention and control of HPV infection in the form of vaccines which look extremely promising, microbicides and, perhaps, correct and consistent use of the male condom especially among adolescents who are already showing evidence of being committed condom users having, unlike most of us in this room, defined their sexuality in the AIDS era.

So thank you very much.

DR. WILSON: Thank you, Dr. Hitchcock.

At this point, I would like to move to the FDA presentations, the first of which would be by Mr. Thomas Simms who is a biologist in the Microbiology Branch.

MS. HITCHCOCK: And I want to thank you for helping me. You were terrific.

FDA Presentations

MR. SIMMS: Good afternoon.

[Slide.]

Before I start, I would like to just take a minute to recognize the people that make up the HPV review team within the FDA. As can be noted from the list, we do have two individuals from CDC, Dr. Katherine Stone and Dr. Elizabeth Unger who serve as consultants for us.

[Slide.]

Why are we here?

[Slide.]

The reason that we are here at the present time is because recently the FDA has been approached by manufacturers requesting guidance for appropriate studies to substantiate new intended uses for high-risk HPV typing assays.

As an example, one of the proposed intended uses is as an initial general population screen for women age 30 and above in conjunction with Pap tests to determine the likelihood of high-grade cervical disease and cervical cancer and the need for appropriate follow up at the discretion of the physician.

We can also foresee in, perhaps, the not too distant future, that this intended use would be expanded to the use of HPV testing without Pap smear, or Pap test.

[Slide.]

We have also been approached about the use of alternate specimen sources. These would be self-collected

vaginal swabs and also the use of urine.

[Slide.]

Everyone has heard a lot of statistics today. I will skip over one or two slides.

[Slide.]

This graph is from the SEER database from the National Cancer Institute. The X axis is grouped on ages. The Y axis is rates per 100,000 individual. For cervical cancer, the incidence, as you can see, starting at age 34, rises up until about the age of 45 and then we get a very slow decline over time.

The mortality associated with it steadily climbs over all these age groups and this age group ends at 85-plus in the SEER database.

[Slide.]

The incident and death rate for cervical cancer. We have all, again, heard a lot of statistics today. This starts off when the SEER database was initiated in 1973. It goes through 1997. We can see the incidence steadily falling over that period of time, the mortality also slightly falling over that period of time.

That has been noted earlier. I have an earlier statistic but the American Cancer Society in 1998 estimated that there would be approximately 13,700 cases of cervical cancer. This ranked cervical cancer as the tenth most

common cancer of women.

[Slide.]

In 1995, Bosch published a study on the prevalence of HPV high-risk types in cervical cancer worldwide. We can see that HPV 16 was the most common at 50 percent followed HPV 18, then HPV 45, and then HPV 31 and the other HPV high-risk types making up the rest of the database.

The mean age for the study group was 47.8 years plus or minus 12.9 years. Although there was a high incidence for HPV 16 and 18, there were also twenty other types that were associated, at least occasionally, with cervical cancer. But they did note a geographic variation within the HPV types.

For example, HPV 45 was the most common in cancers from Western Africa. HPV 39 and 59 were found almost exclusively in cancers from Central and South America.

[Slide.]

What has the FDA approved so far for HPV testing?

[Slide.]

The current approved assay has essentially two indications for use that are of interest to us today. The first is screening patients with ASCUS Pap smear results to determine the need for referral to colposcopy.

The second intended use is in women with low-SIL or high-SIL Pap-smear results. Prior to colposcopy and HPV

result will aid the physician in patient management by assisting with risk assessment.

[Slide.]

The current interpretation of result for testing a women with ASCUS Pap smear is that if the HPV high-risk test result is negative, we believe that there would be a high probability that a higher disease stage would not be found at the time of colposcopy.

But, if the result, the HPV test result, was positive from that group, we believe that there was a low but increased probability that the higher disease stage would be found at colposcopy.

[Slide.]

As part of the database that we reviewed and study that we reviewed for this submission, we grouped individuals out by essentially age groups. On the chart, you can see that we grouped in patients by less than 30 years of age, 30 to 39, and age greater than 39. All these women had consensus of results of either CIN 2 or 3.

Below each age group there are a number of women that comprised those groups, the prevalence of disease being CIN 2 or 3 in those groups. What is probably interesting here is the positive and negative predictive value that we found with the data evaluation, that in that less than age 30 group, we had a positive predictive value for the HPV

testing of 16.8 percent.

We move up to 30 to 39 group, our positive predictive value increased a little bit to 24.7 percent whereas in the age group greater than 39, the positive predictive value fell down to 9.8 percent. The negative predictive value for all the age groups remained essentially the same.

[Slide.]

During the preparation of our talk, we did review some of the current literature. What we found were actually more questions than answers.

[Slide.]

We did note that it does appear that the Pap-test-result terminology does not appear to be consistently applied throughout the literature. When the Pap test is used as part of a studies diagnostic algorithm, there is an issue of subjective diagnostic variation between sites.

You will hear more of that from our statisticians in a minute. Also a large number of the studies used CIN 2 and CIN 3 together as an outcome in grading them as high-grade disease. We have been informed that most CIN 2 lesions will regress. So it would be difficult, or it is difficult, to determine the true impact that HPV testing will have on cervical cancer, we believe.

This may be especially true in studies conducted

in the United States. Since there is such a low prevalence of cervical cancer, what other surrogate markers may we use to determine screening efficiency?

[Slide.]

Other points in the literature; how should the HPV assay's cutoff be established? Should the cutoff be established according to minimal detectable limits which is essentially analytical sensitivity of the assay? Or should the cutoff be established to increase specificity to detect high SIL or cancer?

[Slide.]

It is also noted that an assay's performance characteristic appears to be affected by the number of HPV types detected. There have been several recent papers that suggest perhaps there should be fewer high-risk HPV types tested for and this would increase the sensitivity for the detection.

There is the issue in the literature should only quantitative assays be used for testing. It is essentially a viral-load measurement. A couple of papers do suggest that a high viral load is indicative of high-grade disease.

Should testing be conducted for persistent HPV infection and that there be no clinical interpretation until some amount of time after the reactive results.

[Slide.]

We have also noted several comments from recognized organizations during our review such as the United States Preventive Services Task Force in 1996 stated there is insufficient evidence to recommend for or against routine cervicography or colposcopy screening for cervical cancer in asymptomatic women, nor is there evidence to support routine screening for HPV infection and that recommendations against such screening can be made on other grounds including poor specificity and cost.

[Slide.]

A recent statement from the American Cancer Society concerning HPV testing; at this time, it is not clear how treatment should be affected by this information. HPV testing and typing is not routinely recommended and most healthcare providers do not use this testing.

[Slide.]

A recent statement from the National Cancer Institute; the use of HPV testing for primary population-based screening is not recommended due to low specificity, and particularly among young sexually active women.

[Slide.]

In 1999, the Sexually Transmitted Diseases Division at CDC conducted a meeting with external experts concerning genital HPV infection and sequelae.

[Slide.]

Three issues that this workshop looked at were management options using HPV testing. That was for the triage of women with ASCUS Pap-smear results as an adjunct to Pap smear and the management of women with confirmed CIN.

[Slide.]

Their conclusions and recommendations were that at the present time, other than the triaging of women with ASCUS Pap smear results, there insufficient data to recommend HPV testing routinely for other clinical purposes.

[Slide.]

Probably one of the best review summaries that I have found, or we found, during our preparation for this meeting is a report from the British National Health Service as part of their health technology assessment entitled A Systematic Review of the Role of Human Papilloma Virus Testing within a cervical screening program.

[Slide.]

The report is freely available to the public. It is on the Internet.

[Slide.]

There were eight authors involved with the review. They did look at approximately 2,100 papers. They found that there were essentially--at the present, there are two different assay technologies that appear to be the methods of choice and that is the PCR with consensus primers. These

are primarily home-brew assays. And also the Hybrid Capture II system.

[Slide.]

The objectives of the review were to evaluate the current literature, or concerning the role of HPV testing, in primary screening alone or in conjunction or as an adjunct to cytology, to improve the management of women with low-grade cytological abnormalities and to improve the accuracy of follow up after treatment of preinvasive or early invasive lesions.

[Slide.]

Also to review the methods available for HPV testing and determine their appropriateness for widespread implementation and to determine what future research is required to obtain more reliable answers about the use of HPV testing and cervical-disease screening.

[Slide.]

They did find that, for the potential roles in screening, that being part of a primary screening in women age 35 years and greater that this may be appropriate, that the false-positive rate in this group, false-positive meaning that these were positive results for women not having cancer, is lowest in this group, that for the management of women with low-grade or borderline smears, that they felt there was uncertainty with the test-negative

predictive value in safety with reduced surveillance.

This reduced surveillance would be an issue of women having a normal cytology in undetectable high-risk HPV types, that these women would not be screened again for a much longer period of time, that for the post-treatment surveillance of CIN and early cancer, to monitor for complete excision.

They believe the early results were promising but better-designed studies were needed.

[Slide.]

Their conclusions were that the high-risk HPV testing is more sensitive than cytology for high-grade CIN but it does have a lower specificity. Testing cannot be currently recommended for widespread implementation. But testing may be appropriate in limited situations. These situations would be the management of borderline Pap smears or in order women when regular screening is problematic.

This would be where high sensitivity is needed. Problematic would be in populations such as underserved populations.

[Slide.]

Continuing their recommendations was the larger ongoing and future studies should follow women for a minimum of five years. Consideration should be given to a very large--and by "very large," they specifically stated 100,000

to 200,000 participants, randomized clinical trial to evaluate the effect of HPV testing on cancer incidence and the length of protection afforded by a negative test in conjunction with a negative cytology.

These reviewers believe that perhaps high-SIL and CIN 2 are not appropriate study endpoints, that the only true method to evaluate study outcome was a demonstration of reduction in cervical cancer.

That concludes my part of the presentation. I thank you for your time.

[Slide.]

I would like to introduce Dr. Kristen Meier who will begin the presentation of statistical issues associated with Pap and HPV testing.

DR. MEIER: Thank you, Tom.

[Slide.]

I would like to begin with a quick review of the claims under consideration, just the essence of the claims, which were for women 30 years or greater. The HPV test could be used in conjunction with Pap smears, possibly also used alone in the future to determine the likelihood of high-grade cervical disease and cervical cancer.

[Slide.]

Before discussing what studies are appropriate to support these claims, I think we need to be clear on the

terminology and definitions of performance measures. You can see, the majority of my talk here is going to focus on defining performance measures and what affects them including target condition, working definition of the target condition, test cutoff bias and variation of performance.

I will then touch briefly on using published studies and good design principles.

[Slide.]

There have been numerous studies on HPV in the literature but I have found that there is a lot of confusion due to the fact that a lot of statistics have the same name but are actually defined very differently. One example here is the measure of sensitivity. That can actually mean a lot of different things and I have just written a few examples of what it might mean.

It might mean the ability of a test to detect HPV-DNA, which is more like an analytical sensitivity. It might mean the ability of a test to detect cervical cancer at the time of the test. Or it could be the ability of a test to predict the risk of cancer at some point in the future. Or it could be the ability of the test to detect precursor lesions as determined by cytology and/or histology.

So all these options are under the heading of sensitivity yet they all have very different meanings and we need to be clear. Hopefully, in today's discussions, we

at

will decide which definition is most appropriate to use and then we will all use the same definition.

[Slide.]

The first component that needs to be defined here is the target condition. In other words, what is it that we are trying to diagnosis or against what standard should the performance of HPV be evaluated? What event are we interested in? Is it a cytology event? Is it ASCUS and above? Is it LSIL and above? HSIL and above? Cancer?

Is it a histological event? And what is the time frame we are talking about here? Are we interested in the time of an initial test of biopsy or the status two to five years from now.

[Slide.]

When defining the target condition, we also need to think about how it will be determined in practice; that is, we need to develop a working definition of algorithm, I will call it, for the target condition and that might be based on colposcopy, histology, endocervical curettage, follow up over time.

When developing this algorithm, we need to consider some statistical issues as well. First, the algorithm should provide a final answer that is not subject to variability. Every subject and specimen in the study should be evaluated using the same definition and the

algorithm should be masked or blinded to the new test result.

[Slide.]

In some instances, this last principle is violated. The performance of HPV in Pap-negative women has not been fully established. However, the result of the HPV test is used to determine whether a women should go on for further workup when she has a negative Pap result.

In particular, if a women has a negative Pap and negative HPV result, they are not sent on for further workup yet some of these women could have cancer. If you don't account for these women, then your estimates of sensitivity and specificity could be biased. This is a well-documented type of bias called verification bias.

The problem is that if you don't adjust for this potential bias, your estimates of sensitivity here could be too high and your estimates of specificity could be too low. Two ways come to mind quickly of how you might adjust for this. One, which is a resource-intensive way, is to send all women in the study on for further workup.

An alternative approach is to estimate the percent of Pap-negative HPV-negative with the target condition and then statistically adjust the final estimates of test performance.

[Slide.]

Once the target condition is defined, we need to know how the test cutoff is defined. By "cutoff," I mean the threshold that is used to separate a positive and a negative result. You can vary sensitivity just by changing this cutoff. Again, we need to understand what we mean when we talk about getting a positive Pap result or a positive HPV result.

A lot of these comments pertain particularly to the Pap-positive results here. We need to know what cutoff we are using, first-off. That needs to be made clear. In whatever we use for our definition of positive and negative, we need to be sure to include the unclear cases as well. They can't be discarded.

Alternatively, we might think about performance measures that are more complicated than sensitivity and specificity but also more flexible to include some of these kinds of cases.

Because the performance does change as the cutoff changes, it is really preferred to report an ROC curve or receiver operating characteristic curve which really gives the performance for all possible cutoff values. It is not clear whether the best cutoff in one clinical setting may not be the best cutoff in another clinical setting. In particular here, the best cutoff for the HPV and combined Pap test may not be the best for HPV alone.

[Slide.]

The other advantage of the ROC plot is that it shows the tradeoff between sensitivity and specificity as the cutoff varies. It is really this tradeoff that is important here. I know there tends to be a lot of focus on just sensitivity or just a negative predictive value, for instance, but we really need both sides here.

Just to bring that point home, I have considered an absurd example here. Suppose I have a new test for cervical cancer that always gives a positive result. This new test is useless because the test result is independent of the target condition. However, its sensitivity is going to be 100 percent which, of course, is much better than the Pap test.

You might all say, "Great; let's go with this test." But the piece you have to consider is the specificity of that test happens to be zero. So the point is you need to always be looking both at the pair, sensitivity/specificity.

Obviously, in this case, you can see that this is not a reasonable test. But how different do sensitivity and specificity need to be or what kind of tradeoff can we live with because, again, we can always increase sensitivity by changing the cutoff, but what tradeoff can we really live with in terms of specificity.

[Slide.]

Once the performance measures have been defined, we can then begin to talk about the types of studies desired. Broadly speaking, we would like a study that represents the intended population; that is one with no or minimal statistical bias and that yields precise estimates of performance.

Of course, the difficulties are in the details here. Minimizing bias can be very challenging, and Colin Begg has written a nice article about that. Also obtaining precise estimates of performance when the disease is rare will require very large studies.

[Slide.]

Let's take a closer look at minimizing bias. The data should be representative or typical of the population of interest with respect to the measure of interest here. That is the HPV and Pap result. By "representative," I mean that the distribution of all relevant factors in the study data is the same as that in the population of interest.

It doesn't matter if we do all kinds of fancy statistical analysis to our data. If the data are not relevant, our analyses are not particularly meaningful and can't necessarily be extended to the population we are interested in.

[Slide.]

What are some of these relevant factors? I just came up with a list on my own here, but you might be able to add to some of these. One is the actual device, itself. If I were using the final version of the test, if I were using the established cutoff and has it been used according to labeling.

Another factor to consider is the person receiving the test. Are they representative of the spectrum of disease? Do they cover the range of patient demographics and important covariates?

The person collecting the specimen can be an important factor, be it a physician or a self-collected specimen. The specimen type can be important as well as the specimen-collection device. The specimen storage and handling can play a role and, finally, the person analyzing the specimen, including the lab technician and the cytologist training/expertise.

[Slide.]

When designing a study, we need to know which factors are going to affect the performance of the HPV result and the Pap result and, from those that will affect performance, we need to match those in the study population and the intended-use population. If there is a feeling that a factor does not make a difference, then, ideally, we would have data that actually demonstrates that the factor doesn't

make a difference.

Now, test performance can vary due to some of the factors I already mentioned, and there may be other factors. Some of these are controllable. Others may not be controllable. They might just be inherent in the practical use of the test.

[Slide.]

This next slide this morning--this is a metaanalysis done by Fahey at all of Pap test performance in the literature between 1984 and 1992. So these were the conventional Pap smears. This would not include the ThinPrep Pap results, but what you see here immediately is a very, very wide range of test performance here.

The authors found that sensitivities ranged from 11 to 99 percent, along this axis here, and specificities--these is actually 1 minus specificity here-ranged from 14 to 97 percent. This line here is a summary receiving operating characteristic curve. I don't necessarily endorse the actual approach they used here but I think the point here is that there is a wide variation in Pap performance.

Variation along this line could be explained by a difference in threshold separating positive-negative Pap results. Variation in this direction here, however, could be due to some sort of different factors, different expertise. Obviously, results up here are much better than

the ones down here. I hope my physicians are up in this area, here.

But the point is that there is a wide variability. I don't think it is really reasonable to talk about an average sensitivity and specificity here because there is a natural pairing there that you cannot break. You need to consider it in terms of a summary plot like this.

What this point shows is that it is very difficult--if we are talking about using the HPV test in conjunction with Pap, or even want to compare it to Pap, the question is what is Pap performance. It, again, would lead us to wanting to do larger studies where we can include a wide range of Pap performance and it might be easier to show improvement of the Pap test when you are in this range than when you are up in this range, here.

[Slide.]

Let me just make a few brief comments about using published studies. I think it can be problematic, you need to be aware. The first issue is the poolability of results. You want to be sure, first of all, that there is sufficient detail reported in the literature articles that you can determine whether the same definitions are being used.

Then, of course, results should be similar before they are pooled. Another concern is the transferability of the results. Are the relevant factors similar in these

studies and are they similar to the intended use you are interested in.

Have the data been reported in such a way that it gives you the information you need, for instance, the per-individual information. We would be interested in the Pap versus HPV results. A lot of the literature I have seen don't report the data that way. They report it as Pap versus histology, HPV versus histology.

Finally, there is always the issue of publication bias where non-significant and inconclusive results are typically not reported in the literature.

[Slide.]

In conclusion, let me just suggest some good design principles to support these claims. We think we need to start with a clearly defined meaningful target condition. We need to also begin with clearly defined performance measures. The test in the study should be performed according to labeling, the patient selection and sample source and collection should be formed according to the intended use.

The populations and medical practice should be representative of U.S. populations and medical practice. It would be a multicenter, a multisite, study to cover the range of patients and range of test conditions. Blinding of HPV results, the Pap results and final diagnosis should be

used. Ideally, the study would be prospective so as not to exclude unclear but important cases and to control for other design factors.

[Slide.]

Thank you. The next speaker is Dr. Marina Kondratovich. She will discuss more specific statistical issues.

DR. KONDRATOVICH: Good afternoon.

[Slide.]

It is operative to compare the Pap test alone and the combination of Pap test and HPV test. Therefore, I will consider some statistical issues of the combination Pap test and HPV.

[Slide.]

If we decided that the reasonable measures of effectiveness of the test is sensitivity and specificity, it is necessary to define the target condition of interest disease. This is an example of what we can find in the literature.

Also, it is necessary to define precisely the positive and negative test results. This example is for the positive test results for the Pap test which you can find in the literature.

[Slide.]

Then, sensitivity of the test for detecting the

target condition of interest is estimated as the proportion of women with confirmed disease who are defined as positive by this test. Similarly, specificity of the test is estimated as the proportion of women who are confirmed having no disease and defined as negative by this test.

[Slide.]

Consider a combination of Pap test and HPV test. The combination of a Pap and HPV test is negative if the results of the Pap test are negative and the results of the HPV test are negative. If the results of the Pap test are positive or the results of HPV test are positive, then the combined Pap-plus-HPV test is defined as positive.

You can see that this is a simple table. It is a model of the combined Pap test and HPV test.

[Slide.]

A combination of the Pap test with any test leads to an increase in sensitivity and a decrease in specificity. Indeed, if I consider the disease subject and this is the sensitivity of the Pap test alone where the Pap test is positive, then for the combined test, we need to add the proportion of women who have Pap-negative and some-test-positive.

Therefore, this is the sensitivity of the Pap test alone and this is the sensitivity of the combined test. Therefore, for any test, sensitivity of the combined test,

Pap and some test, is always bigger than the sensitivity of the Pap test alone. Similarly, for known disease subjects, this is the specificity of the Pap test alone where the Pap test is negative. But the combined test is negative only if the Pap test is negative and some test is negative.

Therefore, the specificity of the combined test is always less than the specificity of the Pap test. Even adding to the Pap test a random test which is defined, for example, randomly by the toss of a coin, will increase sensitivity.

Therefore, an increase in combined sensitivity alone does not prove that the combination of the test is effective if the combined specificity is shown to decrease appreciably.

[Slide.]

Now, let us consider how to compare the two tests. We have test A with sensitivity and specificity and test B with each, sensitivity and specificity. If test B has both specificity and sensitivity bigger than for test A, then it is very easy to make a conclusion. Obviously, test B is clearly preferred.

However, in the case of the combined test, we always have that sensitivity of the combined test is bigger than the sensitivity of the Pap test but specificity is lower than specificity for the Pap test. Therefore, in this

situation, it is not clear which test, the combined test or the Pap test, is preferable.

We will consider that the two tests are used in the same population, the same prevalence of disease. We can use, for comparing the diagnostic test, positive and negative predictive value.

[Slide.]

Consider the plain sensitivity and specificity. This point represents the Pap test with sensitivity and specificity. This line represents such tests which have the same positive predictive value like a Pap test alone. This line represents such tests which have negative predictive values the same like the Pap test alone.

Therefore, we obtain four regions. This region represents tests which are overall superior than the Pap test alone. This test has both positive and negative predictive value better than the Pap test alone.

This region represents tests which are inferior than Pap test alone because they have both positive and negative predictive value worse than for Pap test alone. Of course, in this region, we need to make a tradeoff between the positive and negative predictive value because, in this region, the positive predictive value was worse and the negative predictive value is better than for the Pap test alone.

In the situation when we compare the Pap test alone and the combined test, the sensitivity of the combined test is always bigger and the specificity is always lower. Therefore, the combined test can be only in this region. You can see that this region is a very tiny region but, mainly, this region combined test can have both predictive-value positive and negative better than for the Pap test alone.

The combined test can lose very tiny, a very small amount, in specificity in order to be in this region.

[Slide.]

Now, I would like to consider some examples. This study was conducted in South Africa and described in this paper. Let disease be defined as CIN 2 or 3 or cancer and positive Pap test be defined as ASCUS and above. This is the sensitivity and specificity for the Pap test alone, the HPV test of the sample collected by the clinician, HPV test self-collected and the simple combination of the Pap test plus HPV testing of the sample collected by the clinician.

I will use these numbers in the graphic presentation.

[Slide.]

Compare the Pap test alone and the combined, Pap plus HPV. This is the performance of the Pap test, sensitivity and specificity. This is the performance of the

combined test, Pap and HPV. You can see that the combined test is in this region. Therefore, the combined test is worse than the Pap test alone if you compare the positive predictive value and, better, if you compare the negative predictive value.

It means that the Pap test alone is the better for confirming the presence of disease and the combined test is better for confirming the absence of disease.

[Slide.]

Now, let me compare the Pap test alone and the HPV test alone. This is the same performance of the Pap test alone. This is the performance of the HPV test alone of the sample collected by the clinician. This is the performance of the HPV testing, of the sample self-collected.

You can see that, for the HPV test collected by the clinician, the positive predictive value of the combined test is worse and the negative predictive value is better. For the HPV self-collected, worse positive and negative predictive value worse. Therefore, this test is inferior overall than the Pap test.

[Slide.]

It is offered to compare Pap testing alone and the simple combination of the Pap test and HPV. But these models have some deficiencies. First consider the Pap testing alone. The Pap testing alone does not reflect the

current approved practice in the United States.

For example, the HPV test has already been approved to manage a women with ASCUS and above Pap test. When we define the positive or negative test results for the Pap test, for ASCUS, we always have only one value, negative or positive. But if we consider Pap plus HPV approved, then the value of this test depends on the results of the HPV test. It can be sometimes minus, sometimes plus instead of when we have ASCUS, we always kept only one value.

[Slide.]

Because the HPV test has already been approved for use in women with ASCUS and above, the real question is how to evaluate safety and effectiveness of HPV testing in a women with a Pap test within normal limits. That is the mathematical model of a simple combination Pap plus HPV is a suitable model.

The formal model of a simple combination of the results of the Pap test and HPV test cannot reflect the different clinical management of the women which has the Pap test result within normal limits and of the women who has the Pap test result within normal limits and negative HPV results.

Also, in this simplified model, the women who has the Pap test within normal limits and the positive HPV results is categorized by this combined test, Pap plus HPV,

as a patient who already has the target condition of interest disease.

The clinical management of such a patient can depend on the viral load of HPV and other factors; for example, the results of HPV testing during some period of time. This model cannot be reflected in the model of the simple combination of Pap plus HPV.

So a simple mathematical model, Pap test plus HPV, is to simply take the model for how this test can be used in practice.

[Slide.]

The answer to this question, how to evaluate the effectiveness of HPV testing in a women with a Pap test within normal limits can be given by a randomized, prospective clinical trial for the women with the normal results of the Pap test. This clinical trial should evaluate the effect of HPV testing on cancer incidence and should evaluate the length of protection afforded by a negative HPV test in conjunction with the results of the Pap test within normal limits.

Thank you.

The next speaker will be Tom Simms. He will present the questions to the panel.

FDA Presentation of the Questions

[Slide.]

MR. SIMMS: Considering our questions for the panel today should revolve around possible future indications for use. This indication for use is for the use of HPV testing in conjunction with or without the Pap test to determine the likelihood of high-grade cervical disease and cervical cancer.

[Slide.]

The first question we would like panel comment and input on is are these appropriate indications for us. What improvements or modifications would you recommend, if any?

[Slide.]

The next question; what studies would be appropriate to support these intended uses. Should these be cross-sectional, longitudinal or performed using other study designs?

[Slide.]

The next question; what study endpoints are appropriate for use, the results of only Pap-smear readings, colposcopy results, biopsy results. Should they be outcome studies or other?

[Slide.]

Next question; given that U.S. women represent a population that is highly screened by Pap test, what, if any, qualifications should be considered in the use of foreign data.

[Slide.]

Next question; should the assay cut-off selection be adjusted to maximize sensitivity for disease rather than virus? If so, what compromises in specificity may be appropriate?

[Slide.]

Next question; how can published studies be used to support applications. How closely should populations in studies be matched to the proposed intended-use population and what analysis of primary or raw data, if any, is appropriate?

[Slide.]

What labeling would be appropriate for samples with a normal Pap test result but HPV high-risk type being reactive or positive?

[Slide.]

Next question; if the HPV test does not specifically type, should the assay be labeled as presumptive? If not, what other cautions or labeling caveats, if any, would be appropriate? If not, what other cautions or labeling caveats, if any, would be appropriate?

[Slide.]

Last question; what studies would be appropriate for point of care of home collection using self-collected vaginal swabs or alternate-source specimens such as urine?

DR. WILSON: Thank you.

As you can see, we have an ambitious agenda trying to get to those nine questions in the remaining two hours. So, at st point, we are going to move to the open committee discussion.

Open Committee Discussion

DR. WILSON: Tom, if you could put up the first question again, we will go back to that. The portion of the meeting is open to public observers but public observers may not participate except at the request of the Chairperson.

MR. SIMMS: I apologize. We were hoping to be able to have this very first slide up all the time for you but we haven't been able to do that. But I believe you do have it in your binders that you may want to go back to it and refresh yourself.

DR. WILSON: Yes; it is. At this point, I would like to open the meeting up discussion by members of the panel. Who would like to ask the first question, make a comment?

DR. BROWN: I just would open the discussion with a general comment about limiting the testing to women over 30. If our endpoint is CIN 3, I believe that data shows, or studies that have been done, show that a significant proportion of CIN 3 is diagnosed in women under 30, possibly as much as 45 percent. If you are using cancer as an

endpoint, although the SEER data does show that the highest incidence is at 30 and above, when you look at that graph, there are a significant number of women, say, 8 to 10 per 100,000 between the ages of, say, 25 and 30, who do have invasive cervical cancer.

So I would raise the question about using 30 as a cutoff if your endpoint is either CIN 3 or invasive cancer as to how many women between 20 and 30 with these diseases are you going to miss and would that possibly impact on their ability to be treated? If there are any of the epidemiologists in the room who would want to address that.

DR. MYERS: Part of the reason historically that there has been a shift in cancer in younger women is probably due to changes in the incidence of HPV and STDs. Part of it is also something that is just observed with screening that a lot of these incident cases of cancers are cancers that are there in unscreened populations but are asymptomatic and not detected.

Both multiple modeling studies and historical data that has looked at populations that have had screening introduced show that. Basic screening theory says that any screening test is going to preferentially detect more slower-growing lesions, so these cancers that occur in younger women are less amenable to detection by any screening modality.

I think the big concern with extending HPV testing to this population is that the prevalence is significantly higher and that these tradeoffs of sensitivity and specificity are going to be much greater.

It is often helpful to think in terms of absolute numbers instead of relative numbers. If the prevalence of high-grade SIL and cancer in a population is 1 percent, in a group of 100,000 women, that means that a 1 percent increase in sensitivity will detect ten extra cases.

A 1 percent decrease in specificity will lead to 990 extra false-positive results. So there are clear tradeoffs here, both in terms of cost which is outside of the mandate of this panel, but in terms of quality-of-life issues. The question of whether those tradeoffs are appropriate is obviously not an easy one to answer, but I think it is helpful to think in terms of those absolute numbers.

Extending screening to younger women would increase those relative values by at least an order of magnitude.

Laura?

DR. KOUTSKY: I agree with what Dr. Myers just suggested but I also know that the same problems with Pap-smear screening in younger women it is observed there are many more women who have abnormal Pap smears. I guess,

following up on the concern of Dr. Brown is this issue of you may not detect that many more cancers because the problem Dr. Myers mentioned. But this issue of getting early treatment for women with CIN 2 to CIN 3 so that they don't require having a hysterectomy and, therefore, they have their fertility preserved throughout their thirties as women delay their reproductive years.

I think that there are questions--I actually came up with a list a seven questions. I am not sure if I can ask the companies if they have data on these questions, but they are questions that I would say are important in helping us make a decision about whether HPV testing will, indeed, give us gains or really not gains in efficacy over Pap screening.

Is that an appropriate time to ask these questions?

DR. WILSON: You an ask those questions.

DR. KOUTSKY: I think most of these questions would be addressed to people from Digene. There is this issue of do you have any data from your ongoing studies that do suggest that, with HPV testing, you are bringing women to treatment and, therefore, less invasive treatment at an earlier stage when women test positive by HPV versus women referred for repeat Pap screening?

DR. LORINCZ: My name is Dr. Attila Lorincz from

Digene. I want to give a very simple answer which is that we don't have any data specifically looking at younger women that we are willing to share or discuss at this point, since we have not looked extensively at that group. So we would rather pass on that question right now.

DR. KOUTSKY: Actually, Dr. Lorincz, I think you could answer some of these other questions. I think another question that has been raised that would be nice to have some data on is this issue of adenocarcinoma versus squamous-cell carcinoma, what does the Hybrid Capture II test performance look like in terms of picking up adenocarcinomas versus squamous-cell?

DR. LORINCZ: We have not specifically looked at adenocarcinoma separated out in most of the studies, there being fairly small cases. In some of the studies, for example, in the Kaiser study, we believe that, from the small datasets, both from what we have done and what the literature has shown, is that the HPV detectability of adenocarcinomas either adenocarcinomas, themselves, adenosquamous carcinomas or adenocarcinoma in situ are on the order of 90 to 95 percent and certainly match, in every way, the detectability of squamous carcinomas.

But we are not willing to pull those data out separately either because then we would be relying on quite small numbers.

DR. KOUTSKY: Another issue that comes up in Pap follow up is women with abnormal results don't come back for recommended repeat Pap or colposcopy. I think it is because of this knowledge that an ASCUS or an LSIL, clinicians are trying to relieve anxiety and suggest, "Don't worry; you don't have cancer but you need to come back for follow-up Pap."

But there are estimates in the literature that up to 70 percent of women who have an abnormal Pap do not follow up with management. I am wondering if you have any data from your studies that suggest that the follow up to colposcopy, if you are HPV-positive, versus the follow up from Pap to repeat Pap to colposcopy is any better.

DR. LORINCZ: We have actually looked at that in a number of studies. We find that the response to an HPV-positive test or an abnormal Pap test are about the same and that--these were studies so the follow-up rates were typically on the order of 70 or 80 percent.

What we did find, which may or may not relevant, is that, for the control group, the double negatives, when we wanted to get them for colposcopy, there was a very poor response rate typically being less than 50 percent. So there is that issue to consider in terms of trials.

But, for HPV, we don't believe that there is a difference.

DR. KOUTSKY: How about post-treatment? Has HPV testing been used in post-treatment? Do you have any information about whether or not a women who has been Papped, she is going to treatment and she is put back into routine Papping, if three or four years down the road, that a positive HPV test is more predictive of recurrent serious disease than a repeat Pap?

DR. LORINCZ: There have been no formal Hybrid Capture post-treatment trials. The only studies available in the literature are fairly small in number and they do show a utility for HPV. We are looking at the idea of so-called test of cure at a number of sites in the U.S., but those data will not be available for probably two to three years.

DR. KOUTSKY: Just one last question. Can you talk a bit about collection and order of collection? Certainly, probably, the best is to have a liquid Pap and just use residual fluid from that for HPV testing. But, in a situation where there isn't a liquid Pap in both the device that Digene recommends for collecting HPV and the order before or after the Pap specimen.

DR. LORINCZ: Of course, we recommend the brush for direct clinical sampling at the cervix. We have looked extensively at order of collection and find no effect for the first, second or even third sample although, in all of

our studies, the Pap comes first because of the expectation that if there is a deficiency, the Pap should get the benefit of doubt.

With respect to the type of sampling, liquid cytology is clearly a possibility for direct HPV testing and that can be done out of a number of competitive media including the PreservesIt or the CytoRich. So I think that that bears in mind what kind of a screening program might be put in place with HPV.

Certainly one combining a liquid cytology capability with an HPV test would seem to be an optimal strategy.

DR. KOUTSKY: Thank you.

DR. WILSON: Dr. Berry?

DR. BERRY: I have a comment. As one that, roughly speaking, dropped in today from Mars with respect to this question, anyway, and luckily ended here rather than Florida, one of the messages of Dr. Kondratovich is that things get murky when you add one test to another.

We were presented data this morning that suggested, at least, that HPV had greater sensitivity than Pap and greater specificity than Pap. Considering a single test, she indicated that, if that is true, then the test is better. If a company is able to show that, then that should be enough. If the company then gets involved in trying to

show what HPV adds to Pap, that is murky business because of the sensitivity moving in one direction, specificity in the other.

The question, perhaps, should be posed not what does HPV add to Pap but what does Pap add to HPV. That is from Mars.

I do have a question, however, for the panel or anyone. One of the issues that we have been told is that sexual contact leads to HPV can lead to cancer, cervical disease and cervical cancer. An issue to be addressed in this is what is the sensitivity of specificity of number of sexual partners?

If one addresses that, the question is how much does an HPV test add to the number of sexual partners. Has anybody looked at that? I guess not.

DR. FELIX: I think that is just too subjective. It is historical data that, at best, is inaccurate and almost always incomplete because the partners of the partners are not factored in so you can never come up with a complete and accurate history.

DR. COX: No, but you could come up with something. The question is how good is it.

DR. BURK: I think that is just not practical for medical practice to use that as an indicator. I think you can take a rough--as the American College of Obstetrics and

Gynecology places high-risk women so you can maybe dichotomize, but I don't think you can finely tune, nor should you finely tune, that because of the variable. You don't know. A women could be monogamous. Like is not uncommon in South America, you have a lot of women who are monogamous whose partners engage in other activities that develop cervical cancer, HPV and are at risk.

So there your measure would not be of value. So I would suggest that, on the one hand, that is an important risk factor. It certainly is a critical risk factor for HPV, but there are a lot of caveats with that. I would suggest that we not really discuss that further.

DR. KOUTSKY: I was just going to say that might have been useful prior to the sexual revolution when many women and men had only one lifetime partner, one versus any more than that. But I think, at this day and age, the sexual behaviors have changed so much and HPV is so ubiquitous that you are dealing more with probably not so much whether you have been exposed but what other factors either you or exogenous factors influence your risk for cancer.

DR. MYERS: We have done some modeling looking at age of onset of activity which, because of probable biological variations, does make some difference in decreasing risk, but that is almost as problematic as number

of sexual partners.

In the U.S. population, part of the reason that delaying sexual activity also affects cervical-cancer risk is that the hysterectomy rate is so high that women are eliminated from the cervical-cancer risk pool for other reasons.

DR. BURK: Just for number one, to hold the discussion on that, one question is, as we are getting into problems with sensitivity, specificity, although you will lose some sensitivity, we know that the biology of HPV 16 is unique and represents the greatest risk for development of cervical cancer. As we have seen, 50 percent of all cervical cancer worldwide is associated with HPV 16.

So what considerations would we give to a test that would maybe lean on the side of reduced sensitivity but that increased specificity for HPV 16. I am just throwing this out as something to consider since that is, I guess, the critical factor, although the rest of the 50 percent is an important risk factor.

The second thing is in the criteria of the age of 30, is there some kind of analytical data that we have used or is that because it is the third decade of life and it kind of correlates? We have kind of glibly thrown that around. It does correlate. I can understand broadly where that term comes from, but I would like to see a little more

analytical analysis of what the exact age is for a specific cutoff for the test.

DR. FELIX: Actually, I think there is pretty good analytical data regarding why they chose 30. It is just incidence of HPV detection in the various age groups. I believe the data is stratified by every five years, or I have seen data stratified every five years.

Actually, it seems that, at age 35, it goes down to below around 8 percent. So the incidence becomes low enough so that it becomes testable. There is really no magical figure other than just incidence of HPV positivity.

DR. BURK: But, if we are going to be dealing in such numbers as for a test for the population, we should do it by pennies, not by nickels, I think. Maybe 28 might not be different from 30. Those two years would capture a significant number of women.

But I agree with you. We have published one of the first studies where we did this age and we showed that the prevalence in the non-colposcopy clinic declined with age. We actually came up with 35 as the best but, again, that was grouping because of small numbers. I think here we are going to be talking about larger numbers. I would like to see by individual ages.

DR. WILSON: We will need to spend one or two more minutes on this first question as to whether these are

appropriate indications for use. Does anyone have any additional comments because we do need to move on to the next question.

Dr. Brown?

DR. BROWN: One other question. A few people have mentioned the data that shows that, of invasive cervical cancers diagnosed in this country, in the United States, 50 percent, fully 50 percent, of women have not had Pap-smear screening in three years.

I would like to hear, although I think some of the speakers addressed this kind of tangentially in their discussion of HPV testing, a more direct comment on how implementing this test will change that, or what evidence is there that adding HPV testing to Pap smear will get those women to be tested and is there any data showing that.

DR. WILSON: To whom were you addressing that?

DR. BROWN: I don't know if it was Dr. Belinson or Dr. Wright, since they both performed these studies in large groups of women who basically had been unscreened. I don't know if they want to comment on how they see that working in this country where the significant number of women who develop cancer are women who have not been screened with their experiences in those situations.

DR. BELISON: Jerry Belinson from Cleveland Clinic. I think I can address that just maybe tangentially,

if you will. There have been multiple efforts on trying to reach the unscreened population. Certainly, in this country, that seems to hit a stone wall somewhere around 75, 80 percent.

Regardless of what you offer and how attractive you make your point of intervention, 20 percent never seem to show up. If the success of the Pap smear is based on multiple repeats and, per chance, you are able to make some little movement into that unscreened group, it might allow you to make that movement once and not depend on multiple screenings.

DR. MIRHASHEMI: A follow-up on that question. If we end up doing a one-time screen, what is the recommendation of treatment, which is what Dr. Koutsky was pertaining to? So if we are not getting to those 20 percent of patients that we can't properly screen by a Pap smear but maybe we can get them in one time for an HPV-DNA test, what do we do with that information?

DR. WRIGHT: Tom Wright, Columbia University. It is a really controversial issue how much we can make an inroad into the unscreened population in this country by offering either self-collected testing or any other approach that you do.

I think it is clear, though, that many of these women who have not had Pap smears in the last several years

have, in fact, had contact with the healthcare system. A good example is the National Breast and Cervical Cancer Screening Program where, for uninsured women, we offer free mammograms in conjunction with free Pap smears. Only a proportion of the women offered both actually opt to have the pelvic exam.

In New York State, it is about 75 percent of the women who opt to have a pelvic exam and a Pap smear of the women who come for screening with mammography. If would could just make a simple inroad into populations such as that and get those women screened, I think that would increase coverage.

What do you do once you find they are HPV positive is a real issue. I think the simplest thing would be to tell those patients that they are clearly at risk for having cervical disease and that they need a Pap smear and maybe being told that they are at risk, they would be willing to come in for cytologic screening. That would be simplest. The most extensive would be to recommend some form of colposcopy or other workup.

I don't think we know which women will accept and we need additional behavioral studies to look at that sort of.

DR. FELIX: I have a follow-up question on that, Tom. If you are going to address that specifically in that

setting that you gave, that example, which is offering a self test to a population of women who may be reluctant, and you say 75 percent of them opt for a pelvic.

Then you offer them the possibility of a self-collected test which will evaluate only HPV, how many of that 75 percent will opt for that not-as-sensitive test, according to your study, than a physician obtained HPV and Pap combined instead of obtaining the physician exams?

In other words, you want to make sure that the 75 percent that you are reaching doesn't turn into 20 percent.

DR. WRIGHT: I agree with that. We do not know those numbers and that is one of the things I think additional research is needed on, to look at those issues.

DR. KOUTSKY: Back to the questions which I am assuming have to do with the previous slide which, to me, the language got shifted for the use of HPV testing in conjunction with or without all age groups, Pap smear to determine the likelihood of high-grade cervical disease and cervical cancer, I didn't understand that, on the table, we have HPV testing alone in all age groups.

DR. WILSON: The first question is for use in conjunction with Pap smear age greater than 30 years or without Pap smear. I believe that is in all age groups; is that right, Dr. Gutman?

DR. GUTMAN: Yes. Actually, before you move to

Question 2, we would sort of like an informal survey of which of those indications the members of the panel think are a good idea. So, if you wouldn't mind a poll, we would be grateful.

DR. KOUTSKY: Could you state those?

DR. GUTMAN: We will show them. We will put them back on the screen and I apologize for the confusion. There was some language that was changed as we moved toward the panel.

DR. KOUTSKY: So there are two questions there on the table.

DR. GUTMAN: That's right. So you get to say they are both good, one is good and other is not, or one is good with the following modifications or both are good with the following modifications, or something totally different.

DR. WILSON: In the interest of time, why don't we just go quickly around the members of the panel starting with Dr. Wendel regarding those first--dividing that into the two uses for the use of HPV in conjunction with Pap for patients greater than 30 years or without Pap in all ages, of those two what you think. Just a brief comment about that.

DR. WENDEL: I guess that, at this point, I am still struck by the lack of enough data to make a decision. So I am not sure what kind of answer you are looking for, a

yes or a not?

DR. WILSON: Whether or not these are appropriate indications.

DR. GUTMAN: This doesn't depend on the existence of data. The next question will be, then, what data supports the claim. This is just a reasonable claim.

DR. BERRY: So the question is is this endpoint of cervical disease and cervical cancer--is that the appropriate endpoint? I assume that if a company looks at a population, whatever the age distribution, the indication would be for that age distribution. So it is kind of a red herring, I think, the first part.

I do think a critical question is is this the right endpoint, cervical disease or cervical cancer.

DR. WILSON: Dr. Weinstein?

DR. WEINSTEIN: I would support that. I am not sure what to say about this question because I was struck by the statistical presentations, in particular sensitivity for what, for what disease or what entity are we making judgments about sensitivity? The other issue is the target condition.

I think until there is a some consensus about what those endpoints should be, it is very hard to come to grips with the possible indications.

DR. WILSON: Dr. Wendel, were you finished?

DR. WENDEL: I can't answer the question. I have the same problems. There are too many things in there on which to base a single yes or no. It is about four or five questions in there, really.

DR. BURK: Let me make a comment on the endpoint. The endpoint, I think--the ultimate endpoint that is clear is the reduction of the incidence of cervical cancer and the reduction of mortality from cervical cancer. I think we would all agree that that is the ultimate endpoint.

So then the question comes, and I was thinking about this--obviously, we can't use that in this day and age. So then there needs to be an intermediate endpoint. So then is it the reduction of CIN 3 in the screened population from the unscreened population.

I am not clear. I haven't thought through this enough to really think about it because you are going to be detecting CIN 3, CIN 2. There is nothing wrong in ablating or treating the true precursor lesions even if they are not your end-stage or your target endpoint. So these are just some things to think about for further discussion.

I guess, in the future indications, I am disappointed that we don't include this negative predictive value possibly in the language of increasing the screening interval. I think for the protection of U.S. women, a woman with a negative Pap smear and a negative HPV test, I am more

comfortable with.

I have more trouble, as we have seen in the statistical analysis and in our discussions, in how we are going to deal with even what the endpoints are in the test, the interpretation and the management of a positive test. So I am a little disappointed that we didn't include that.

DR. GUTMAN: You can add that.

DR. BURK: I guess I would support HPV for adding to the Pap test for the negative predictive value of two negative tests and possibly for the increase in the screening, or pulling those women out of the normal population. If you had to do one test in a population of women who were not going to come back for treatment, although I guess my bias is not to set policy for patients' lack of compliance but, in any event, I think that there is data and, certainly, there are preliminary studies in the sense that would be an indication.

The role for some age above 30 for adding it for screening where you really increase the specificity due to do drop in the HPV test, I agree that I am a little skeptical because of the lack of complete data. But I guess I would lean more on favoring the addition in some older age group.

I would not favor, at this point in time, the blanket screening of HPV testing in all age groups. I am

concerned about your detecting 60 percent, if you are doing yearly screening, in women under the age of, say, 25 where we know what the incidence and prevalence rates are going to be.

Certainly, where the cumulative prevalence rates are going to be above 50 percent, I think it would have little value.

MR. REYNOLDS: As all of you know, I am not a clinician so I am looking at this from a little bit different point of view from the rest of you. In so far as using it in conjunction with the Pap test, I think we all agree that there is some value there. The question that Dr. Brown brought up, which is for those people who are not currently screened, who are not getting the Pap, how is this going to affect them?

If a self-directed test, even though we know that the data on that is not as good as the Pap, would be used by these people who don't currently get a Pap, at least they are getting some type test with the possibility that that would then spur them to follow up.

I know we have seen this in health screens for males with PSA where we have offered PSA blood testing and they will tell you right up front, "Okay; I am willing to have some blood drawn, but I don't want that digital-rectal exam." Right up front, they will tell you that.

But yet, when they get a positive PSA, they will come and see a physician and go through follow up. So if you are going to say that a self test is available and, admittedly, it may not be as good as a Pap, at least if that population is not currently being screened is willing to screen themselves and then do follow up, I think there is some value to that.

DR. FELIX: I second the motion to add an indication for a negative HPV test and a negative Pap. The data there seems the strongest. There is a fair amount of data from the U.S. which is, I think, a very critical source for what we are considering, that indicates that a double-negative test has an extraordinarily high negative predictive value.

So I would urge an indication for that in lengthening the screening interval. I would, at this point, not advocate a self-test until sociological studies are performed to assure that what will happen is not a shift from medical intervention to a self intervention rather than accessing the non-screened population.

For the last five years, I have been very active in attempting to reach the unscreened and have been completely unsuccessful at doing that regardless of incentives, programs, et cetera. We have had very little success and we have tried everything from peer groups to

nurses to friends, et cetera, and different strategies.

The unscreened women is an extraordinarily difficult patient to access. So I would like a lot more sociological data before indicating the test for self-testing rather than going ahead and offering it.

DR. MYERS: As a decision analysis, I think these indications are certainly reasonable. There are just tradeoffs associated with all of them. I agree with adding an indication for lengthening interval.

I think you could also make an argument, in a women with a history of normal Pap tests and a double negative, to stop screening after a given age. I think a women in her 60's who has had a life time of normal Pap smears and is negative for HPV has, essentially, no risk of cervical cancer and could be dropped from the screening pool

But, to my mind, the question isn't so much are these appropriate indications as that it becomes an a policy analysis and a tradeoff analysis.

The other concern that I have is that I don't see much point in having a specific indication for age because it is clear, both from other interventions and physician compliance with recommendations from panelists that physicians are going to do what they think is appropriate. I find it very hard to imagine that physicians who feel that it is appropriate to use this test on women under 30

wouldn't do so.

MR. RELLER: Unless I am missing something, the logical follow-through on these comments is that every women in this country, perhaps without regard to age, should have HPV testing. That may be wise, but I haven't seen an analysis of data that convinces me that the benefits of that are sufficient to undertake it now.

I can see utility for this test. If one wanted to exclude past exposure which gives no prediction of future exposure, a entity that may be present and goes away, that waxes and wanes with a long interval and a test as presented currently that includes, but does not denote, those types that are most associated with later invasive disease.

So the last part of this, that it could be used to determine the likelihood of high-grade cervical cancer down the line, I just don't see--it may be very helpful to exclude, put in a very low probability, but to predict what is going to happen based on this test as so far presented with the one-time cross-sectional assessment, I am very skeptical.

So I honestly do not think that I have seen enough data to make it perfectly clear to me exactly how this potentially useful test should be deployed and the data that would enable one, from a public-health standpoint, to deploy it with great conviction that the additional good contrasted

to what is available now is definitely going to be achieved.

DR. HAMMERSCHLAG: As a pediatrician, this is a little bit out of my field as well, but, from looking at the data presented, it would seem that it has more value as an exclusionary test than prospectively. I think I would concur with Dr. Reller. I am just not sure what we would do with it.

Things are just a little too confusing. The question of what we are comparing it to, the issue of what does the sensitivity really mean, comparisons, maybe, if other tests were available, then they should be compared head to head.

So, at this point, it appears that if you are double-negative, negative HPV and negative Pap, certainly that is good exclusionary criteria for however you want to use it. I guess if you are a 60-year-old woman and you have been negative for a while, to continue screening might be rather futile. It is not going to really yield very much. Certainly our energy should probably be directed towards the other end and there, of course, we have the problems as have been mentioned by some of the other panelists which I don't think I need to add to.

DR. WEINSTEIN: I would concur with the last two comments. I guess the one other issue that I am a little bit concerned about is that, based on what we heard earlier

today, much of the disease, much of cervical cancer, in the United States comes from people who may be in medically underserved populations.

And then we just heard some comments that, no matter what you do, you can't get about 20 or 25 percent of individuals, perhaps from those same populations, to come for testing. So, it calls into question, in my mind, what the ultimate benefit is of having a new and better test if you can't get the people who are going to get the disease to come for testing in the first place.

DR. TUAZON: I agree with the previous three panel members, but the issue is, you know, screening this people--is it cost-beneficial to screen everybody and do the HPV, to make a decision in terms of extending their visits or their testing.

The other point is those who are Pap-smear negative and HPV-positive, what do we do with those patients right now? Are these people--we know that they are at risk. What do we do in terms of their actual management? Do you do a PCR to pick up the ones that are more likely to be at high risk of developing CIN or carcinoma?

So those are some of the issues that I would like to raise.

DR. BERRY: I read this question very differently from many of the panel members. I read it simply as saying

what does a company have to do to show that HPV should be approved? With respect to that, I would like to, and I hope the FDA does simplify the question and drop these ages, both ages, and let us focus on is it an appropriate indication to address high-grade cervical disease and cervical cancer?

My answer to that is yes. That is not an easy answer to come by from me. I am pretty hard-nosed with respect to the eventual benefit that Dr. Burk was indicating with respect to mortality. For example, my answer would be just the opposite if we were talking about prostate cancer and PSA screening, which makes enemies in my home institution.

But, in this case, Pap smears have shown dramatically that we can reduce mortality by finding this disease at an early stage. So I think surrogate endpoints are completely appropriate and I think that the FDA should approve studies that address the surrogate endpoints indicated here.

DR. BROWN: I would just make a comment about the endpoints that Dr. Burk raised. The whole reason that the Pap smear has decreased mortality is because cervical cancer, unlike many cancers, does follow a continuum where there is a set of preinvasive stages before it becomes invasive and that is why the mortality has been able to be decreased because you are finding the preinvasive--that is

your endpoint, ideally, is the preinvasive disease which you then treat and eradicate thereby preventing invasive disease so I think, as a surrogate endpoint, really is the endpoint, is the preinvasive state of cervical cancer. That is completely appropriate.

I guess I would say, though, based on everything we have heard today, the strongest evidence that hits me in terms of an immediate application is for the question of changing screening recommendations, I can tell you that, as a member of many of these organizations and knowing that expanding the screening interval has been shown to be possible, it is certainly not the rank and file opinion of obstetricians, gynecologists, family practitioners and so on in this country, still the idea that Pap smears need to be done every year.

Looking at a cost issue, I think that using this combination in terms of its negative predictive value as a way to increase the screening interval for women safely and, therefore, freeing up money and resources to be able to use on some of these other questions, I would certainly support that.

I think in terms of just using it instead of Pap smear in all age groups, I would have to concur with the other speakers and say that right now, there doesn't seem to be enough clear evidence to say that is an appropriate

indication but that it should be studied because it seems that it may be useful.

DR. DURACK: I can only comment that I think the question is extremely complex as it is asked, and we are in a difficult situation to try to give "an" answer. I would just make a comment to try and simplify a little bit. Let's imagine the Pap smear didn't exist. We have a test that performs well and we would certainly use it and deploy it, so we really have two good tests.

The question then becomes how do we utilize two good tests most effectively. That is a very, very complex question. To answer it, I believe, we would need more data from the fourteen studies that are listed as complete or nearly complete. To answer it without having those data, not just in the form of a summary table but in actually seeing the data I think is really difficult.

So I think we need those data and then I think we need to have a more formal analysis of the scenarios, particularly the effect of the false-positives and the increased number of reactive tests that would be performed on those false-positives before we can make a recommendation.

Probably, after that, we would need to have some form of additional study to look at the actual effect of using these tests. So I am sorry that I can't give a yes or

no answer. I think that we have a good test and that it is going to be used in some way, but how to say this is the way to use it today is, I think, beyond what we can do right now.

I think we can ask for those data and we can be sure that we are hard-nosed about asking for the analysis of the effect of increased false-positives.

DR. KOUTSKY: I actually do think that there is a potential use of HPV testing in women over the age of 30 and, as much as I know that once you put an age of over 30, it is sort of meaningless, I still think there is such a major difference in the epidemiology of HPV infections in the late teens or twenties and above age 30, I think that, in addition to the data we saw presented today, there are also plenty of other studies suggesting the utility of HPV testing in women over the age of 30.

So I think that there is an indication. There is certainly still a need for more data but, to me, the data are all very promising suggesting use of HPV testing in an older group of women.

I think the issue of younger women is very difficult with the current formats for the tests in light of the somewhat lack of specificity but I think that that should continue to be an issue that is discussed because I think there is, also, a potential with possibly a different

HPV test to have utility in younger women.

I would just like to comment about this issue of overtreatment that always seems to come up, that we are referring a lot of women for unnecessary treatment. I think, although we don't have data for this, but one possibility in the treatment of women with intraepithelial neoplasia is you are actually reducing the risk for subsequent acquisition within transformations on epithelium.

It could be that, in light of the sexual revolution in the '60s, '70s and '80s without the amount of screening and treatment of the cervix, we would have even higher rates of cervix cancer. These are unknown questions, but I think they are all possibilities in light of the early age at which we are seeing high-grade disease and cancer.

DR. MIRHASHEMI: I agree with the other panelists. I also want to confirm that, really, the surrogate endpoint may be important to identify the cervical dysplasia and the precursor lesions because we know this disease is a stepwise process.

In terms of the question of HPV screening in conjunction, I think, again, I agree with the other panelists, the confirmation of two negative tests may be an interesting issue to look at. What do you do with a Pap-negative HPV-positive test is, I think, a loaded question.

With regards to using the Pap test to determine

high-grade cervical dysplasia without the Pap smear, again, I am a little reluctant to answer that question at the present time. I don't think we have enough data.

DR. WILSON: Just as a corollary, the second question is if the data are not sufficient for us to really answer the first question, then what data do we need? What types of studies would be appropriate to support these? Should these be cross-sectional, longitudinal, performed using other study designs? Do any of the panel members have any brief suggestions as to study design?

Dr. Burk?

DR. BURK: I made my comment. The problem is that CIN 3, as the true cancer precursor--I mean, one of the things that, hopefully, we will define in the future of research is which CIN 2 and CIN 2 represent true cancer precursors. Right now, we don't know that and we know that many CIN 1 and CIN 2 are just transient lesions.

But there are some which are cancer precursors. We know that CIN 3, by and large, is an important cancer precursor. That, to me, would represent an intermediate endpoint but, then, do you look at detection of it or prevention of it in your screened and unscreened population.

DR. WILSON: Mr. Reynolds

MR. REYNOLDS: I have no comments at the study design at this time.

DR. WILSON: Dr. Felix?

DR. FELIX: I think that it is pretty clear to me that, if we are going to answer these questions, and we are all going to come up with important questions, particularly later on, about the indications we have made, we need prospective studies. I don't think you can answer these questions without prospective studies.

If you are going to prolong screening intervals, it is critical to have data after the prolongation of the screening interval in the population in which you choose to prolong the screening interval. The data doesn't exist yet. Therefore, we need that study and that data.

As far as the type of study, I think that Dr. Belinson has set a very important standard in that study in China. I hesitate to demand that kind of study because it is extraordinarily resource-intensive, but his study has demonstrated an enormous false-negative rate in previous gold standard which is colposcopy.

I saw some of this data be presented. It is not published yet, so I don't want to quote the exact numbers, but along the lines of 20 percent or around that, the false-negative rate for colposcopy. Therefore, some consideration has to be given to insuring truth as biopsy sample not colposcopic sample in prospective studies.

It could probably be done if not for the entire

population, at least for a sample of the population, to be able to estimate the false-negative rate of colposcopy and extrapolate the true disease from the entire population.

As we move forward, I think that all studies intervening in this field will have to, I think, demonstrate that.

DR. WILSON: Dr. Myers?

DR. BURK: I have to leave. I had given my written comments on the questions that were addressed to us before.

DR. WILSON: Thank you for attending.

DR. MYERS: I agree with the comment. I think all study designs have some value, but I think that some prospective data is very helpful. I think, as one of the authors of one of the reports that showed a lower sensitivity for Paps, based on studies that did have a histologic confirmation of a percentage of the test-negatives that I think it is only fair that, if we are going to use that example of the low Pap sensitivity, that we judge new technologies by the same criteria.

The other thing that I think we desperately need are measures of quality of life or patient preferences for all the different options because it is very difficult, in trying to put together the different possible policy options, to really assign any value to them that are

meaningful to patients.

DR. WILSON: Dr. Reller?

DR. RELLER: I don't have anything to add further.

DR. WILSON: Dr. Hammerschlag?

DR. HAMMERSCHLAG: Same. I really don't have anything to add.

DR. WILSON: Dr. Weinstein?

DR. WEINSTEIN: The only comment would be the one that I made earlier about defining disease. There needs to be a consensus about that and I think I would leave that to the experts.

DR. WILSON: Dr. Tuazon?

DR. TUAZON: No comments.

DR. WILSON: Dr. Berry?

DR. BERRY: I agree with Dr. Myers about the possibility of a number of studies. I would prefer prospective longitudinal studies. I think the focus should be on strategies. I do want to make one comment about Dr. Meier's presentation which I agree with completely.

She addressed something called verification bias. She indicated that, in order to address it in the study, one should send all women for further workup including HPV-negative, Pap-negative. She indicated that would take a lot of resources.

I hope the FDA does not insist on extensive

investigation and Pap-negative and HPV-negative. It is asking a lot of women and it might even prohibit studying the question. Instead, I hope the FDA allows for reference to historical information or, if it does insist on prospective information regarding this group to allow for sequential design to look, let's say, only at the first set of women in the trial who are HPV-negative Pap-negative to address the question of what the colposcopy further investigation shows.

So a number of possible designs but don't take too seriously the need for resources.

DR. WILSON: Dr. Brown?

DR. BROWN: I would just echo what one of the other speakers said about the need for prospective trials and, also, bring up the issue of the endpoint being CIN 2 or CIN 3. I didn't hear much discussion here today but I know that in the literature there is this question of persistence of HPV infection and I think that we need to see more data about that, serial testing for HPV and what does that predict more who is going to get CIN 3 that does go on to become cancer.

DR. WILSON: Dr. Durack?

DR. DURACK: My comment is just to reinforce a point we heard this morning from one of the presenters which I thought was quite powerful. What is our real object here?

Our object is not to produce a better test. It is to reduce the rate of cervical cancer. I think, in order to achieve that, prospective longitudinal studies are essential. The field is big enough and important enough that we will probably be happy to accept a lot of other kinds of trials but, as others have said, we will have to go with the prospective studies.

DR. WILSON: Dr. Koutsky?

DR. KOUTSKY: I would second the need for prospective studies. I also would like to see more U.S. data. I think that the differences in the way screening is used--although the underlying epidemiology of the disease, I think, is pretty similar with subtle differences worldwide. There are very different screening practices, very different ways of reading Paps, very different ways of reading biopsies and I think it would be good to have data, more data, from the U.S.

DR. WILSON: Dr. Mirhashemi.

DR. MIRHASHEMI: I pretty much agree with the rest of the panel. I just want to reiterate what Dr. Simms said earlier about the National British Health Study and their recommendation to look at prospective studies, randomized, multi-institutional and very large numbers. I think we need to look at thousands and hundreds of thousands of patients. I think that is going to be critical to answer these

questions.

DR. WILSON: Thank you. The third question is a little bit of a spinoff from the second question in that what study endpoints are appropriate for use, the options being the results of Pap-test readings, colposcopy, biopsy or outcome studies. We have heard at least some comments that there should be a histologic correlation with biopsy because of potential false-negative colposcopy.

Do the panel members agree with that or does someone feel there should be other endpoints? Dr. Wendel?

DR. WENDEL: I think Dr. Brown addressed that issue very thoroughly that it really is the need for biopsy. The biggest question is which of the CINs is the most important stage and do we know enough to pick out which of the CIN 1s is the one you can follow, which of the CIN 2s you can follow. But I agree that a surrogate of a preinvasive lesion is most appropriate for the longitudinal U.S. studies.

DR. WILSON: Does anyone on the panel dissent with that view or are there any additional comments that anyone would like to make?

DR. BERRY: You don't want to biopsy HPV-negative Pap-negative.

DR. FELIX: I disagree

DR. WILSON: Dr. Felix?

DR. FELIX: I disagree. I don't think that we have proven, at all yet, in the U.S. that Pap-negative HPV-negative are free of disease. We have proved it in China in a group of 2000 women who have never been screened. But I don't think we have proven it in the U.S. in a group of women that have been screened.

DR. BERRY: How can you run a study with informed consent that will accrue patients under that circumstance?

DR. FELIX: We have done it at USC. We had a group of women who we consented for biopsies up front. There are new biopsy techniques, as was indicated, that are much less painful than the standard Schubert instrument to take biopsies.

These are relatively tolerable procedures and women do agree to be followed at biopsy when explained that there is a 20 percent false-negative rate in the gold standard.

DR. BERRY: Women are much more magnanimous than men.

DR. WILSON: Let's move on to the fourth question, then, which states, given that U.S. women represent a population that is highly screened by the Pap test, what, if any, qualifications should be considered in the use of foreign data. Starting with Dr. Wendel?

DR. WENDEL: I think the main issue would be the

durability of the negative predictive value of the negative-negative tests that have been talked about, and does that apply in the United States as it applies in those other populations.

MR. REYNOLDS: As a couple of other speakers have already indicated, sometimes the screening procedures and the like may not be the same in some of these foreign countries. I do think there has to be consideration in looking at foreign data that you may be comparing apples and oranges and that everything may not be done the same way that it is done here in this country.

MR. SIMMS: Dr. Felix?

DR. FELIX: I actually think that in most of the international studies that have been done, it has been verified with U.S. methods. But the biggest bias that I see in the foreign data is that the patient population is different. The only population that comes close are the northern European studies but, even then, they have longer screening intervals than U.S. women.

I believe that the women who has been screened four or five times and has been negative all four or five times and has dysplasia is a very different person and has a very different disease than the women who has not been screened and has been tested at that point.

To me, the answer of whether HPV can detect that

particular patient has not been demonstrated so I think that we need to do the tests in well-screened U.S. population women.

DR. WILSON: Dr. Myers?

DR. MYERS: I concur. I think the foreign can help inform the design of the U.S. study but they need to be replicated in the U.S. population.

DR. WILSON: Dr. Reller?

DR. RELLER: It has been emphasized earlier the importance of the endpoints other than invasive cervical carcinoma and death in outcomes. Clearly, for all the reasons mentioned, that is important but one of the things that seems to me is in U.S. populations is to see what effect the different potential strategies has ultimately on the disease. Does it really reduce further or not, and that it is looked at. Are there strategies that would reduce it further to get at these currently unmet or undetected people who escape care and end up with the disease that theoretically should not occur.

DR. WILSON: Dr. Hammerschlag?

DR. HAMMERSCHLAG: I concur with the previous comment.

DR. WILSON: Dr. Weinstein?

DR. WEINSTEIN: I have nothing to add.

DR. WILSON: Dr. Tuazon?

DR. TUAZON: I don't have anything to add.

DR. WILSON: Dr. Berry?

DR. BERRY: Same.

DR. WILSON: Dr. Brown?

DR. BROWN: Nothing to add.

DR. WILSON: Dr. Durack?

DR. DURACK: Nothing.

DR. WILSON: Dr. Koutsky?

DR. KOUTSKY: Nothing to add.

DR. WILSON: Dr. Mirhashemi?

DR. MIRHASHEMI: Nothing.

DR. WILSON: Okay. We will move on to the fifth question which states, should assay cutoff selection be adjusted to maximize sensitivity given that we have heard from FDA that there are multiple definitions of sensitivity. If so, what compromises in specificity might be appropriate.

Dr. Wendel?

DR. WENDEL: No comment.

DR. WILSON: Mr. Reynolds

MR. REYNOLDS: Nothing.

DR. WILSON: Dr. Felix?

DR. FELIX: No comment.

DR. WILSON: Dr. Myers?

DR. MYERS: I don't think we have the data to answer that. I don't think that is a question for this

panel, actually.

DR. WILSON: Dr. Reller?

DR. RELLER: Given the potential differences in test performance with cutoff values and inclusion of the multiple types, it seems to me that the answer to this question lies in how do you plan to deploy the test. I mean, if it is too negatives, if you want the emphasis on ruling something out, then you are going to go for sensitivity.

If you are using it as a confirmatory test, or a tie-breaker with an abnormal, then you may want to--if you have what you think is otherwise a sensitive test, you may lean towards specificity. So I think the answer to this question depends on what the strategy is and how the test is deployed.

DR. WILSON: Dr. Hammerschlag?

DR. HAMMERSCHLAG: I think this is really a technical issue which I don't think we really are approaching here on test performance in that way.

DR. WILSON: Dr. Weinstein?

DR. WEINSTEIN: I agree.

DR. WILSON: Dr. Tuazon?

DR. TUAZON: I don't think we have any information to answer that question.

DR. WILSON: Dr. Berry?

DR. BERRY: I disagree. I think it is a very important question that should be addressed by really every such test. The issue of the tradeoff between sensitivity and specificity is a very difficult one that should be addressed by companies as well as they can in presenting to the FDA. There is clear tradeoff. The tradeoff has to do with consequences. What are the consequences of false-positives in this disease They may be different than in breast cancer than in HIV than in other circumstances and these should be addressed.

I think that companies that come forward should actually do outcomes research that look at quality of life, address these questions, address the ROC curve, the plot of sensitivity and specificity and make proposals to the FDA and a panel such as this decide what is appropriate.

In fact, of course, the individual women may have her own sensitivity and specificity tradeoffs. We can't get to that level but we can, as a public group, make decisions that help these women.

DR. WILSON: Dr. Brown.

DR. BROWN: I would agree that it is an important question but I don't think we were presented with enough data today to comment on it.

DR. WILSON: Dr. Durack?

DR. DURACK: Again, no specific answer but just a

brief comment. I think we have heard several themes this morning which would emphasize that specificity should be preserved as much as possible in this as we go forward, as we make the tradeoffs.

DR. DURACK: Dr. Koutsky?

DR. KOUTSKY: I would agree with the last comment and also just I think given that we have got a couple of different options for how this test is used, it would seem to me that the tradeoffs between sensitivity and specificity may be different based--would certainly be different based on how the test was finally proposed to be use.

DR. WILSON: Dr. Mirhashemi?

DR. MIRHASHEMI: I also think it is a very crucial issue for the panel but, unfortunately, we didn't see any data today and we can't make any recommendations at the present time although there is some data out there.

DR. WILSON: Thank you. Let's move on to the sixth question which states that how can published studies be best used to support applications. The first part is how closely should populations and studies be matched with the proposed intended-use population, the second part being, what analysis of primary or raw data, if any, is appropriate.

Dr. Wendel?

DR. WENDEL: I don't think I have any comments to

at

add.

DR. WILSON: Mr. Reynolds

MR. REYNOLDS: Obviously, the population that we are studying should, as close as possible, resemble the population that it is intended for use. I think we would all agree with that.

As to the second part of the question, I think that is going to take more time than we have right now to really consider how you want to approach that second part of the question.

DR. WILSON: Dr. Felix?

DR. FELIX: I have already offered my opinion regarding which population. Pertaining to that, I think that the current studies would be best to use to guide the future studies and can be relied upon to make assumptions about the test and the people with the disease that could certainly facilitate the future studies.

Again, I emphasize the need for U.S.-screened women. As far as the analysis presented to this panel, I have had various experiences in FDA analysis and always think that having the raw data available is of significant importance.

DR. WILSON: Dr. Myers?

DR. MYERS: I don't have anything to add.

DR. WILSON: Dr. Reller?

DR. RELLER: Ideally, studies are designed to answer a question or questions and to try to use the published information to answer a different I think is problematic so that there are some gaps in what we know and I think it will take additional prospective studies in appropriate populations to get the appropriate answers.

DR. WILSON: Dr. Hammerschlag?

DR. HAMMERSCHLAG: I have nothing to add.

DR. WILSON: Dr. Weinstein?

DR. WEINSTEIN: Nothing to add.

DR. WILSON: Dr. Tuazon?

DR. TUAZON: Nothing to add.

DR. WILSON: Dr. Berry?

DR. BERRY: As closely as possible, of course. How should they be analyzed? Dr. Myers will not be surprised to hear me say that they should be analyzed using a hierarchical Bayesian approach, Bayesian metaanalysis. Yes; raw data, if they are available. However, the raw data is not as valuable if they are not covariates, patient characteristics, that come with it.

DR. WILSON: Dr. Brown?

DR. BROWN: Nothing.

DR. WILSON: Dr. Durack?

DR. DURACK: Nothing.

DR. WILSON: Dr. Koutsky?

DR. KOUTSKY: Nothing.

DR. WILSON: Dr. Mirhashemi?

DR. MIRHASHEMI: Nothing.

DR. WILSON: Moving on to the seventh question, it states, what labeling would be appropriate for samples with normal Pap test results but HPV high-risk type reactive.

DR. FELIX: Could somebody from FDA clarify that question.

DR. WILSON: Thank you. Mr. Simms, could you clarify that question for us, please?

DR. GUTMAN: I actually think you have already alluded to this issue which is what happens when there is a tension between the Pap result being negative and the HPV being a positive signal. Frankly, I would be happy to see you skip that question and go on to the eighth. It has already been discussed from my perspective

MR. REYNOLDS: I just have one question regarding this. We do that not all types of HPV are necessarily associated with cervical cancer. So if we are not identifying what type it is, you could be positive for a type that is not associated with cervical cancer.

DR. HAMMERSCHLAG: But I understand that is not in the Digene panel so it is almost meaningless unless you really start getting into broadly-reactive type-specific tests that give you--

DR. WILSON: Let's move on to the eighth question. If the HPV does not specifically type, should the assay be labeled as presented or as a screening test. If not, what are the cautions or labeling caveats, if any, that would be appropriate? Dr. Wendel?

DR. WENDEL: I think that is sort of the same issue as the last question.

DR. WILSON: Mr. Reynolds, do you have a comment

MR. REYNOLDS: No comment.

DR. WILSON: Dr. Felix?

DR. FELIX: I think that I see less of a problem with this than with the other previous seven questions. The fact that the test doesn't specifically identify any given high-risk HPV type, to me is not a problem because all of the studies that have been done have been done with this medium. So the results, the predictability, the risk of the women or the absence of risk of the women that we are seeing in these studies are all done with this cocktail approach.

Therefore, the term "high-risk" types as a generic term I think quite appropriate. I don't see a program needing to limit the indications because it doesn't specifically detect any high-risk type.

DR. WILSON: Dr. Myers?

DR. MYERS: I agree.

DR. WILSON: Dr. Reller?

DR. RELLER: I like the concept of screening as opposed to presumptive because I don't think that it is--presumptive--I mean, you can say that there is evidence of infection or not with risks, with a virus that is associated with an undesired outcome, but you can't presume something from the test.

DR. WILSON: Dr. Hammerschlag?

DR. HAMMERSCHLAG: To me, again, this is just sort of the flip of the previous question, the phrasing of looking at it the other way, and probably moot since the medium or the test that we are discussing contains really only high-risk types to begin with.

So, unless we are getting into something that is much more broadly reactive, hypothetically, another test, it really doesn't mean very much.

DR. WILSON: Dr. Weinstein?

DR. WEINSTEIN: I concur with that comment.

DR. WILSON: Dr. Tuazon?

DR. TUAZON: I agree.

DR. WILSON: Dr. Berry?

DR. BERRY: Nothing to add.

DR. WILSON: Dr. Brown?

DR. BROWN: Nothing.

DR. WILSON: Dr. Durack?

DR. DURACK: Nothing.

DR. WILSON: Dr. Mirhashemi?

DR. MIRHASHEMI: Dr. Koutsky had to leave but she wanted to make the comment that she did not see any reason for it to be labeled as presumptive. And I agree.

DR. WILSON: I don't have a copy of the ninth question. Could you put that up, please.

DR. GUTMAN: We would actually like to defer the ninth question. I would like to introduce a tenth question, instead, just to make sure that I am getting the message here. So we will take the ninth question off. You are welcome to submit comments after the panel on where we should go with the ninth question.

We really take seriously our charge to be least burdensome, and you have put some very interesting and demanding things on the table. If they are fair and square, they are fair and square. I thought I heard a fair amount of enthusiasm for additional American data, for prospective data and, possibly, at the most extreme, for biopsying negative patients, all of which, frankly, are at the edge of what we usually would ask for.

I want to make sure that I have captured that one or more sponsors might be very interested in pushing forward with claims based on the existing published data. That should be an option for them. I want to make sure I have captured the essence. It sounds to me like if that were

brought back to this panel, you might not be incredibly enthusiastic about that route.

I would really appreciate getting some sense for the panel so that we don't miscue to any of the sponsors in the audience how far we would allow them to go off of the published data and the claims.

Obviously, anybody can strengthen the claims, clarify the claims, present the data in a more cogent manner. You have heard some of the literature. You know some of the literature. Does anybody have an opinion about whether this would make a good--what we would call a paper PMA, a PMA based on literature rather than based on additional data.

DR. WILSON: Does anyone have any comments in response to that?

DR. BERRY: I do.

DR. WILSON: Okay. Dr. Berry?

DR. BERRY: Naturally, the devil is sometimes in the details and I would want to see the details. But, frankly, and I was one of the people that said prospective, longitudinal--frankly, the case presented, even though nothing I have said so far has been related to the specifics of the case presented, the case presented today, I thought, had the foundation for being quite credible.

Even though I certainly would not be ready to vote